PERGAMON

Neuroscience and Biobehavioral Reviews 24 (2000) 27–30

NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS

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Clinical psychopharmacology of AD/HD: Implications for animal models

M.V. Solanto[1,*]

The Mount Sinai School of Medicine, Division of Child and Adolescent Psychiatry, Box 123, New York, NY 10029, USA

Abstract

A working knowledge of the clinical psychopharmacology of the psychostimulants in AD/HD is essential to the development of valid animal models of the disorder. The clinical pharmacokinetics and pharmacodynamics of D-amphetamine (D-AMP) and methylphenidate (MPH) have been well-studied. The plasma half-life of these compounds in children is approximately 5 h, with an onset of therapeutic action within a half-hour, and peak action at 1–3 h. The effective dose range for D-AMP in children is 0.2–0.5 mg/kg, and for MPH 0.3–1.0 mg/kg. In humans, psychostimulants bring about reductions in activity level and impulsivity, and improvement in attention span. Enhancement of executive processes mediated in the pre-frontal cortex in humans (especially tolerance for delay) is believed to mediate these therapeutic effects. There are no long-term remedial effects of the drug on behavior—i.e. symptoms return when the drugs are withdrawn. When used in the therapeutic dose range, there is no evidence of the development of significant tolerance or sensitization. These and other clinical findings to be discussed must guide and constrain the development of animal models of stimulant drug effects in AD/HD.

Keywords: AD/HD; Psychostimulants drugs; Methyelphenidate; Review

1. Introduction

Despite their widespread use in the treatment of Attention Deficit/Hyperactivity Disorder (AD/HD)[1], the mechanisms of action of the psychostinulants, methylphenidate (MPH) and dextro-amphetamine (D-AMP) remain poorly understood. Animal models offer the possibility of understanding neurobiological processes, which cannot be readily studied in humans. Development of these models, however, must be guided and constrained by a working knowledge of the clinical psychopharmacology of AD/HD.

2. Acute clinical effects

Numerous studies, based on parent and teacher ratings, direct clinical observations, and laboratory tests, have shown that the psychostimulant drugs bring about significant reductions in the two major AD/HD symptom clusters of inattentiveness and hyperactivity-impulsivity. These studies have also shown that stimulants bring about improvement in problems commonly associated with AD/HD, including poor performance on academic tasks [36], aggressive behavior [16], parent–child interaction problems [5], and social unpopularity [47]. A recent review [38] concluded that 70% of outpatients experience clinically significant improvement when treated with a given stimulant. An earlier report [14], had shown further, that when a carefully titrated trial of each stimulant was administered to each subject, nearly all children 98% in a sample of 48 with AD/HD) responded to either MPH or D-AMP.

The calming effect of the stimulants was once thought to be 'paradoxical,' or opposite to the activating effect expected in normal individuals. A pivotal study in 1978, however, [30] demonstrated that D-AMP had qualitatively similar effects in normal and AD/HD children and in normal adults, in that *all three groups* showed significant decreases in activity and impulsivity, and increases in attentiveness following drug administration.

3. Pharmacokinetics

The pharmacokinetics and pharmacodynamics of psychostimulants in clinical use have been well studied. The effective dose range in children is 0.3–1.0 mg/kg for MPH and 0.2–0.5 mg/kg for D-AMP. Therapeutic action is rapid and short-lived, with onset within 30 min, peak effects at about 2 h, and maximal duration of 5 h [27]. Despite consistency of group response and generally linear improvement with increasing dose in the therapeutic range [36], the response of individual children to MPH or D-AMP varies widely both within and across behavioral domains [32], and

* Corresponding author. Tel.: +1-212-241-5420; fax: +1-212-831-2871.
E-mail address: mary_solanto-Gardner@mssm.edu (M.V. Solanto)
[1] Also at Albert Einstein College.

0149-7634/00/$ - see front matter
PII: S0149-7634(99)00061-5

neither body weight [31] nor blood level [27] has utility in predicting the most effective dose. Further, as many as 25% of all children with AD/HD may respond preferentially to one psychostimulant over the other [14].

4. Long-term clinical effects

Although children with AD/HD are typically treated for periods of several years, sometimes extending into adolescence, there is no systematic evidence to date of the development of tolerance or of sensitization ('reverse-tolerance'); effects of the drugs given acutely and given after chronic treatment appear to be similar. Concomitantly, there is no long-term remedial effect of the drugs on behavior—i.e. symptoms return when the drug is discontinued.

5. Neuropsychological and neurobiological substrates of clinical effects

Neuropsychological, neurophysiological, and neuroimaging studies in individuals with AD/HD have attempted to ascertain the fundamental cognitive and behavioral processes which are altered by psychostimulant treatment, and the corresponding neurobiological mechanisms of stimulant drug action. Numerous studies have demonstrated that methylphenidate improves performance on laboratory tests of reaction time [41], sustained attention [23], and focused attention [12], and produces corresponding enhancement of the P300 component of the event-related EEG potential [22], an index of allocation of attentional capacity. More specific studies of information-processing suggest that the beneficial effect of stimulants is specific to the response-organization rather than stimulus-evaluation stages of processing [45]. Although some studies have shown improved performance on measures of paired-associate learning [40] and more complex learning tasks [46], more robust effects of stimulants are shown on measures of retention [15] rather than acquisition in children. Methylphenidate's positive effect on measures of working memory [42] and motor inhibitory control [44] indicate improvement in executive functions which may be the key to methylphenidate's therapeutic effectiveness. Significant stimulant-mediated reduction in 24 h motor activity and restlessness, including activity during sleep [29], however, suggests that reduction in hyperactivity is a primary effect of the stimulants rather than simply a by-product of enhanced concentration or inhibitory control.

The results of neuroimaging studies of children with AD/HD are now converging in revealing abnormalities in the anterior frontal cortex and basal ganglia—areas primarily responsible for executive function and motor control, respectively. Early studies of regional cerebral blood flow revealed hypoperfusion in the right striatum [24], with increased perfusion following a dose of methylphenidate. More recent anatomical MRI studies have shown reduced volume in the right anterior frontal cortex [11,21] as well as in caudate [4,11,21], and globus pallidus [4,11], particularly on the right [11], in children with AD/HD. Of particular interest in the sample studied by Castellanos and colleagues were significant (negative) correlations between performance on inhibitory tasks and the volume of the three brain regions (predominantly on the right) which differentiated the normal control and AD/HD groups [7], providing support for the functional significance of the neuroanatomical findings. PET studies have, disappointingly, not revealed effects of acute [26] or chronic [25] MPH or D-AMP treatment in any brain region beyond what might be expected by chance.

6. Mechanisms of action

Elucidation of the CNS mechanisms of therapeutic action of the psychostimulants has been the goal of considerable thought and debate [8,28,35,39]. Research in animals has established that at the cellular level both MPH and D-AMP potentiate the action of dopamine and norepinephrine in the synapse by facilitating release, blocking re-uptake, and to a lesser extent, inhibiting the catabolic activity of monoamine oxidase [18]. Systematic clinical trials in children comparing selectively noradrenergic and dopaminergic agents have shown that the most effective drugs are those which, like the psychostimulants, have effects on both catecholamines [49]. Research in monkeys by Arnsten [2] and Aston-Jones [3] indicates that noradrenergic pathways from the locus coeruleus to the pre-frontal cortex are important in mediating selective attention, inhibitory control, and working memory. Dopamine, on the contrary, is found in nigrostriatal and mesocorticolimbic pathways, which are important in the regulation of motor activity [33]. Dopaminergic neurons proceeding from the ventral tegmental area forward to the nucleus accumbens via the medial forebrain bundle mediate the rewarding effects of pleasurable stimuli and of psychostimulant drugs [17]. Stimulant effects on activity in animals are biphasic with lower doses of D-AMP (0.5–2.0 mg/kg) or MPH (4–5 mg/kg) increasing locomotor activity, and higher doses (5–10 mg/kg for D-AMP and 8–16 mg/kg for MPH) decreasing it, concomitant with pronounced increases in stereotypic behaviors.

Any attempt to explain the neuropharmacological mechanisms of action of stimulants in the treatment of AD/HD must grapple with the fact that the primary effect of MPH and D-AMP is to increase locomotor activity in animals. Several hypotheses have been proffered to resolve this apparent enigma. Among these are that the reduction in activity level and increase in attentional focus seen in children are comparable to the reduction in activity secondary to stereotypy following high stimulant doses in animals. Several studies of divergent thinking and cognitive perseveration, however, have indicated that the therapeutic effects on attention and activity in children are not

associated with increased cognitive constriction or stereotypic thinking [13,37,43]. An alternative hypothesis is that the reduction in activity level in children is mediated by stimulation of inhibitory pre-synaptic autoreceptors, which reduce dopamine activity and thereby compensate for excess dopamine activity in AD/HD. Some support for this possibility has been provided in research in which very low MPH doses of 0.1 mg/kg—thought to be in the very low range (approximately 0.25 mg/kg) shown to stimulate autoreceptors in animal research with D-AMP [6,19]—also reduced activity in children with AD/HD [34]. Further support comes from recent research in which levels of the dopamine metabolite HVA in CSF were positively correlated with severity of hyperactivity in AD/HD children, and also significantly predicted a positive response to methylphenidate treatment [9,10]. The hypothesis that the therapeutic effects of psychostimulants involve dopaminergic pathways, which mediate reward [20] received support in a study in which MPH increased the effort children expended in order to obtain reward on a progressive ratio schedule [48]. The fact that psychostimulants do not have euphorigenic effects in children, however, is inconsistent with the hypothesis that their therapeutic effects are mediated by stimulation of endogenous reward pathways.

7. Validity of animal models

Clearly, much research is necessary to elucidate the therapeutic mechanisms of stimulant drug action. Integration of pre-clinical and clinical research has the potential to considerably advance our understanding in this area. The foregoing suggests that in order to adequately mirror the clinical phenomena of drug response in AD/HD, animal models must be characterized by the following: (1) increased 24 h locomotor activity ('hyperactivity') as well as deficits in stimulus control of behavior ('attention') and inhibitory control ('impulsivity'); (2) amelioration of these deficits by stimulants in doses comparable to those used clinically; (3) immediate onset of action and absence of tolerance or sensitization with repeated administration; (4) absence of long-term remedial effect of drug treatment; (5) effects on both dopaminergic and noradrenergic receptors and pathways; (6) qualitatively similar behavioral effects of drug treatment in the animal model and in normal control animals. Animal models meeting these criteria afford the possibility of yielding unprecedented insights into the neurobiology of AD/HD and its pharmacological treatment.

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